PATENT COOPERATION TREATY

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INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Form PCT/IPEA/416
RG/G-32855A/BCK		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/EP2004/000456	21.01.2004	22.01.2003

International Patent Classification (IPC) or national classification and IPC
A61K9/20

Applicant
SANDOZ AG

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 6 sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:
   a. ☒ *sent to the applicant and to the International Bureau)* a total of 3 sheets, as follows:
      ☒ sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).
      ☐ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.
   b. ☐ *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or tables related thereto, in computer readable form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).

4. This report contains indications relating to the following items:
   - ☒ Box No. I Basis of the opinion
   - ☐ Box No. II Priority
   - ☐ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - ☐ Box No. IV Lack of unity of invention
   - ☒ Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - ☐ Box No. VI Certain documents cited
   - ☐ Box No. VII Certain defects in the international application
   - ☐ Box No. VIII Certain observations on the international application

Date of submission of the demand	Date of completion of this report
13.08.2004	21.03.2005

Name and mailing address of the international preliminary examining authority:

European Patent Office - P.B. 5818 Patentlaan 2
NL-2280 HV Rijswijk - Pays Bas
Tel. +31 70 340 - 2040 Tx: 31 651 epo nl
Fax: +31 70 340 - 3016

Authorized Officer

von Eggelkraut-Gotta

Telephone No. +31 70 340-4732

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/EP2004/000456

Box No. I Basis of the report

1. With regard to the **language**, this report is based on the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This report is based on translations from the original language into the following language , which is the language of a translation furnished for the purposes of:
   - ☐ international search (under Rules 12.3 and 23.1(b))
   - ☐ publication of the international application (under Rule 12.4)
   - ☐ international preliminary examination (under Rules 55.2 and/or 55.3)

2. With regard to the **elements*** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

   Description, Pages

   1-11 as originally filed

   Claims, Numbers

   1-32 received on 13.08.2004 with letter of 23.07.2004

   ☐ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing

3. ☐ The amendments have resulted in the cancellation of:
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

* *If item 4 applies, some or all of these sheets may be marked "superseded."*

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	7,8,16,17,22,23,25-29
	No:	Claims	1-6,9-15,18-21,24,30-32
Inventive step (IS)	Yes:	Claims	25,26
	No:	Claims	1-24,27-32
Industrial applicability (IA)	Yes:	Claims	1-32
	No:	Claims	

2. Citations and explanations (Rule 70.7):

see separate sheet

Re Item V.

1 The following documents are referred to in this communication:
D1 : US 5 442 008 A (FUELBERTH WERNER ET AL) 15 August 1995 (1995-08-15)
D2 : DE 44 20 102 A (ASTA MEDICA AG) 14 December 1995 (1995-12-14)

2 INDEPENDENT CLAIM 1

2.1 The present application does not meet the criteria of Article 33(1) PCT, because the subject-matter of claim 1 is not new in the sense of Article 33(2) PCT.
Document D1 discloses (the references in parenthesis applying to this document): Tablets comprising ramipril and lactose monohydrate, maize starch, microcrystalline cellulose, highly disperse silica or mannitol and microcrystalline cellulose (examples 6, 7). The problem of the influence of humidity is addressed (column 1, line 60 - column 2, line 24).

2.2 The present application does not meet the criteria of Article 33(1) PCT, because the subject-matter of claim 1 is not new in the sense of Article 33(2) PCT.
Document D2 discloses (the references in parenthesis applying to this document): Tablets comprising ramipril, microcrystalline cellulose, Starch 1500, lactose, disperse silica (example 8).

2.3 The excipients used in the ramipril formulations are mostly known from D1-D3. The a particular brand name can not confer novelty because the product of a brand name may change over time and the name is as such unclear. The composition claimed comprises dry mixed excipients being identical to those disclosed in the prior art. Consequently, the subject-matter claimed can not be rendered novel by the water content which derives implicitly from the water content of said same excipients.
As the same excipients are used in the prior art and the present invention, the water content of the final formulation is most important, as also can be derived from the arguments put forward in the application. However, the application does not give statistical data of the KF values cited. Furthermore, no KF values are given for the formulation prepared in the examples, but only LOD data is provided. Consequently,

it is not possible to compare the formulations of the present application and the prior art as to their water content, this being an essential feature of the invention.

3 INDEPENDENT CLAIM 30

3.1 A package as in claims 30-32 does not render a product novel which lacks novelty as such, if the package as such is also not novel.

4 DEPENDENT CLAIMS 2-24, 31, 32

Dependent claims 2-24, 27-29,31, 32 do not contain any features which, in combination with the features of any claim to which they refer, meet the requirements of the PCT in respect of novelty and/or inventive step (Article 33(2) and (3) PCT). As claims 27-29 may also relate to the mere process of packaging of the composition, said claims are not novel.

5 CLAIMS 25 and 26

5.1 The present application seems to meet the criteria of Article 33(1) PCT, because the subject-matter of claims 25 and 26 is inventive in the sense of Article 33(3) PCT. The process for the preparation of a composition comprising

ramipril under the conditions set out in claim 25 and 26 can not be derived from the state of the art.

Claims

1. Solid pharmaceutical composition comprising
   (a) an effective amount of ramipril and/or a pharmaceutical acceptable salt thereof and
   (b) one or more pharmaceutically acceptable excipients,
   characterized in that the composition is stabilized by having a suitably low water content of less than about 4.0 weight-% measured by loss-on-drying or of less than about 5.5 weight-% measured by Karl-Fischer-analysis.
2. Composition according to claim 1, wherein the water content is less than about 4.5 weight-% measured by Karl-Fischer-analysis.
3. Composition according to claim 1, wherein the water content is less than about 3.0 weight-% measured by loss-on-drying.
4. Composition according to any of the preceding claims, wherein ramipril and/or a pharmaceutical acceptable salt thereof is in form of pharmaceutically acceptable anhydrate, solvate and/or, hydrate and/or in crystalline and amorphous form.
5. Composition according to any of the preceding claims, wherein the pharmaceutical composition is a tablet.
6. Composition according to claim 5, wherein the tablet is suitably coated to generate a filmcoated tablet and/or a pill.
7. Composition according to claim 1 – 4, wherein the pharmaceutical composition is a capsule.
8. Composition according to claim 1 – 4, wherein the pharmaceutical composition is a sachet.
9. Composition according to any of the preceding claims, wherein the excipients have a suitably low water content.
10. Composition according to claim 9, wherein one of said excipients is microcrystalline cellulose.
11. Composition according to claim 1 - 9, wherein one of said excipients is Avicel PH 112.
12. Composition according to claim 9, wherein one of said excipients is starch.
13. Composition according to claim 1 - 9, wherein one of said excipients is Starch 1500 LM.

14. Composition according to claim 9, wherein one of said excipients is silicon dioxide.
15. Composition according to claim 1 - 9, wherein one of said excipients is Syloid AL-1 FP.
16. Composition according to claim 9, wherein one of said excipients is calcium hydrogen phosphate.
17. Composition according to claim 1 - 9, wherein one of said excipients is Dicafos A or A Tab or Anhydrous Emcompress.
18. Composition according to claim 9, wherein one of said excipients is lactose.
19. Composition according to claim 1 - 9, wherein one of said excipients is Pharmatose DCL 21.
20. Composition according to claim 9, wherein one of said excipients is mannitol.
21. Composition according to claim 1 - 9, wherein one of said excipients is Perlitol.
22. Composition according to claim 9, wherein one of said excipients is calcium sulphate.
23. Composition according to claim 1 - 9, wherein one of said excipients is Destab or Drierite.
24. Composition according to any of the preceding claims where one or more excipients are dried prior to use or throughout the manufacturing process to achieve the required level of water content.
25. Process for the preparation of a composition according to any of the preceding claims, wherein environmental conditions during manufacture are maintained at a relative humidity equal or less than 35% at ambient temperature.
26. Process for the preparation of a composition according to claim 1 - 23, wherein environmental conditions during manufacture are maintained at a relative humidity equal or less than 35% at equal or less than 30° C.
27. Process according to any of the preceding claims, wherein the pharmaceutical composition is packaged into a packaging material suitably tight against penetration of humidity.
28. Process according to claim 27, wherein the packaging material is a container including lid composed of polyethylene and/or polypropylene and/or glass.
29. Process according to claim 27, wherein the packaging material is a strip or blister pack composed of aluminium which might be suitably coated or high density polyethylene.

30. Package comprising a composition according to claims 1 - 23 packaged with packaging material suitably tight against penetration of humidity.
31. Package according to claim 30, wherein the packaging material is a container including lid composed of polyethylene and/or polypropylene and/or glass.
32. Package according to claim 30, wherein the packaging material is a strip or blister pack composed of aluminium which might be suitably coated or high density polyethylene.